REMARKS

Entry of the foregoing and reexamination and reconsideration of the subject application, as amended, pursuant to and consistent with 37 C.F.R. § 1.112, are respectfully requested in light of the remarks which follow.

At the outset, Applicants thank Examiners O'Hara, Seharaseyon and Spector for the courtesy of the interview held on April 10, 2003, and their helpful comments.

I. STATUS OF THE CLAIMS

As properly noted in the Office Action Summary, claims 35-58 stand pending and claims 52-57 stand withdrawn as drawn to a non-elected invention. Claims 31-51 and 58 are currently under examination and were rejected.

Applicants have amended claims 35, 41, 42, 50, and 58. The amendments to claim 35 can be found in the specification at least in the examples and claims originally filed and has been drafted following the suggestions of the Examiners. Claim 41 was amended to place "herniated disc" in the singular and not in the plural. Claim 42 has been amended to recite "presents as sciatica" to more precisely claim the invention. The amendment to claim 50 deletes a typographical error and introduces no new subject matter. The amendment to claim 58 changes a claim dependency.

Applicants introduce new claims 59-82. These new method claims all depend from previously examined claims. Therefore, these new claims should present no additional search burden. Support for these claims can be found at least in the claims originally presented in the PCT application, as well as throughout the specification.

Applicants cancel claims 38, 44 and 45 without prejudice of or disclaimer as to the subject matter contained therein. Applicants also cancel claims 52-57 at this time, as these claims are drawn to non-elected subject matter.

The amendments to the claims have been made without prejudice of or disclaimer as to the subject matter contained therein. Applicants maintain the right to file continuation or

divisional applications on the canceled subject matter. No new subject matter is believed to have been introduced by entry of this amendment.

II. STATUS OF THE APPLICATION

Applicants note the acknowledgment of the IDSs filed January 17, 2001 and June 28, 2002. Applicants respectfully request consideration of the IDS submitted February 27, 2003 in the Office's next action.

Applicants acknowledge acceptance by the Office of the priority statement and that a certified copy of the Swedish applications will be requested by the Office from the International Bureau if necessary.

Applicants note that the restriction requirement has been made final despite Applicant's traversal.

Applicants note that the objections to the specification have been withdrawn. Applicants further note that the rejection of the claims under 35 U.S.C. § 112, second paragraph were withdrawn in view of Applicants' last response.

III. CLAIM OBJECTIONS

Claim 49 stands objected to because of the second recitation of "is administered" in the claim. Applicants reviewed claim 49, but note that the objected to phrase appears to be in claim 50. Accordingly, Applicants have amended claim 50 (not claim 49). This amendment should moot the objection.

IV. SCIENTIFIC BACKGROUND ON NUCLEUS PULPOSUS MEDIATED DISORDERS

An understanding of nucleus pulposus and how it acts to cause disorders is needed to distinguish the claimed invention from the prior art. One nucleus pulposus mediated disorder is sciatica. The word "sciatica" is derived from the Latin word "ischii" which means located in the region of the hip. The peripheral nerve that runs in the leg from the level of the pelvis down to the knee is called the "sciatic nerve". The pain associated with sciatica is typically

felt in the hip, buttocks and/or leg. However, sciatica is not associated with peripheral nerves, including the sciatic nerve. Unfortunately, the radiating pain felt in the leg with sciatica was first considered to be local inflammation of the sciatic nerve, hence the name "sciatica". Today, sciatica is known to be a problem linked to the intraspinal nerve root, which is not part of the peripheral nervous system and is not a peripheral nerve. Thus, although the term "sciatica" lives on, it is not at all related to the sciatic nerve, and the sciatic nerve has nothing to do with the condition of sciatica.

Sciatica and other nucleus pulposus induced nerve disorders cannot be classified as a neurodegenerative disorder. Neurodegenerative disorders are hereditary or sporadic conditions which are characterized by progressive nervous system dysfunction. These disorders are often associated with atrophy of the affected central or peripheral nervous system, mainly the brain. Sciatica and nucleus pulposus induced conditions do not involve atrophy of the nerve tissue. Nucleus pulposus induced conditions are not hereditary, caused by a metabolic process, or caused by infection. Examples of neurodegenerative conditions include: motor neuron disease (*e.g.*, amyotrophic lateral sclerosis), Alzheimer's disease, and Parkinson's disease. Thus, neurodegenerative conditions clearly would not include nucleus pulposus induced disorders such as sciatica.

Instead, nucleus pulposus mediated disorders relates to intraspinal nerve root exposure to the nucleus pulposus. The presence of constriction or compression of the nerve is not required for the disorder to manifest itself. It was the discovery that exposure of the intraspinal nerve root to the nucleus pulposus material (*i.e.*, the jelly-like disk tissue) resulted in a reduction in motor nerve conduction in the **absence of mechanical compression** of the nerve. This reduction in motor nerve conduction is characteristic of sciatica and other nucleus pulposus mediated disorders. It is the contact with the jelly-like nucleus pulposus tissue, or components therein, which cause the disorder. No nerve compression, constriction, or nerve injury is necessary for reduction in motor nerve conduction velocity or to cause sciatica. In fact, exposure of a peripheral nerve to nucleus pulposus does not cause any

irritation to the peripheral nerve. *See* Rydevik *et al.*, 1983, *Acta Orthop. Scand.* 54(4): 670-71 (attached).

Thus, none of the references cited by the Office relate to nucleus pulposus mediated disorders whatsoever, as the conditions discussed by the references do not involve any nerve root exposure to the nucleus pulposus jelly-like material.

V. REJECTIONS UNDER 35 U.S.C. § 102

Claims 35-37 and 45-51 stand rejected under 35 U.S.C. § 102(e) as purportedly anticipated by Amin *et al.* (U.S. Patent No. 6,319,910, hereinafter "Amin"). Amin purportedly discloses "that chemically modified tetracyclines, including doxycycline, are a class of non-steroidal anti-inflammatory drugs which inhibit TNF-α, and can be used for treating diseases or disorders associated with elevated activities of TNF-α." Amin also purportedly discloses "an effective amount of a chemically modified tetracycline used in a method for treating a disease or disorder associated with elevated levels of TNF-α, including neurodegenerative disorders, that the invention is particularly useful in the treatment of humans, that the active principal may be administered by any means that achieves its intended purpose such as parenteral routes, subcutaneous, intravenous, intradermal, intramuscular, orally and other routes, and that the dosage administered will be dependent upon the age, sex, health and weight of the recipient, kind of concurrent treatment, frequency of treatment and nature of the effect desired, and that the most preferred dosage will be tailored to the individual subject, as is understood and determinable by one of skill in the art, and the dosage may be 100 mg." Office Action, page 5.

1. Traversal of Rejection

Applicants respectfully disagree and assert that neither a *prima facie* case of anticipation nor obviousness has been adduced. To anticipate a claim, a single source must contain **all** of the elements of the claim. *Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986). Missing elements may not be

supplied by the knowledge of one skilled in the art or in the disclosure of another reference. *Structural Rubber Prods. Co. v. Park Rubber Co.*, 749 F.2d 707, 716, 223 U.S.P.Q. 1264, 1271 (Fed. Cir. 1984). Moreover, a reference must also be read for what it **teaches as a whole** and not for what it teaches in isolation. *Hybritech*, 802 F.2d at 1383, 231 U.S.PQ. at 93.

Although Amin is asserted as teaching all the elements of the claimed invention, it in fact does not. Amin does not teach the alleged method of treating a neurodegenerative disorder with a TNF-α inhibitor. Within the section cited by the Office (*i.e.*, col. 5, l. 65 to col. 6, l. 24) is the stated following:

> Non-limiting examples of **diseases and disorders associated with enhanced COX-2 activity** and elevated levels of COX-2 products treatable by the method of the present invention include brain ischemia, inflammatory bowel disease, **neurodegenerative disorders**, and cancers such as adenomatous polyposis, colon cancer, breast cancer and prostate cancer, etc. **Non-limiting examples of diseases and disorders associated with elevated levels of TNF-α** treatable by the method of the present invention include multiple sclerosis, septic shock, periodontal disease, graft-vs.-host disease, cerebral malaria and cachexia associated with cancer or HIV infection. Accordingly, the method of the present invention can be used to prevent, inhibit, or alleviate such COX-2 and/or TNF-α related conditions. (Emphasis added) Col. 6, ll. 18-31.

Thus, neurodegenerative disorders are linked to elevated levels of COX-2 activity and not with elevated levels of TNF-α activity. Therefore, the conclusion that this reference teaches a method of treating neurodegenerative disorders with TNF-α inhibitors is wrong. Amin teaches the use of COX-2 inhibitors to treat neurodegenerative disorders and not TNF-α inhibitors. Additionally, Amin does not teach or suggest using TNF-α inhibitors of any type to treat **any nerve disorder**, let alone a neurodegenerative disorder or a nucleus-pulposus mediated disorder.

2. Traversal of Rejection in view of Claim Amendments

Applicants have amended the claims to be directed to methods of treating nucleus pulposus mediated nerve disorders. In the event that the Office may consider asserting the Amin reference to the amended claims, Applicants will address the rejection. Amin does not teach or suggest the treatment of nucleus pulposus mediated disorders with a TNF-α inhibitor. Amin also does not teach the treatment of sciatica, a nucleus pulposus mediated disorder, with a TNF-α inhibitor. As discussed above in Section IV, a nucleus pulposus mediated injury is not a neurodegenerative disorder. Therefore, no association between nucleus pulposus induced nerve disorders and neurodegenerative disorders would have been made by the artisan of ordinary skill nor should be made here.

In fact, Amin teaches away from the claimed invention as amended given the discussion on nitric oxide ("NO"). Amin teaches that the methods and compositions disclosed are for use in treating diseases and disorders in which TNF-α and/or the products of COX-2 are elevated, but not the level of NO. *See* Amin at col. 6, ll. 15-18. It is known that the level of NO is increased in the spinal nerve root tissue after exposure to nucleus pulposus. M. Kawakami *et al.*, 1999, *J. Bone & Joint Surgery*, 17:941-946, Abstract (attached). Accordingly, a nucleus pulposus mediated disorder would result in both increased NO and an introduction of TNF-α. Therefore, based on the teachings of Amin, treating a nucleus pulposus induced disorder with a TNF-α inhibitor would not be recommended, let alone concluded by the artisan of ordinary skill.

Applicants conclude the Amin does not teach all elements of the claims, either as amended or in their previously presented form for at least the reasons stated above. Additionally, Amin teaches away from the claimed invention. Thus, for at least these reasons, the rejection under 35 U.S.C. § 102(e) should be withdrawn and the claims allowed.

VI. REJECTIONS UNDER 35 U.S.C. § 103

Claims 38-51 and 58 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Amin *et al.* (U.S. Patent No. 6,319,910, "Amin") in view of Sommer *et al.*, 1997 *Neuroscience Lett.* 237: 45-48 (hereinafter "Sommer").

Amin *et al.* is cited for the reasons discussed above. As asserted above, Amin fails to teach the invention either as previously presented or as currently amended. Certainly, Amin does not disclose treatment of any conditions mediated by nucleus pulposus. Additionally, even if neurodegenerative disorders were to encompass nucleus pulposus mediated disorders (which they do not for the reasons discussed above), Amin does not teach or suggest the treatment of neurodegenerative disorders with TNF-α inhibitors or any disorder with both increased TNF-α and increased NO.

The reference by Sommer is cited by the Office for purportedly disclosing "that inflammatory nerve pain from lepromatous leprosy is associated with a massive increase in the production of TNF, and that the pain can be dramatically reduced by inhibitors of TNF production." Office Action, page 7. Sommer also purportedly discloses "that TNF levels are increased in experimental neuropathies, such as nerve crush, chronic constriction injury (CCI, a partial nerve injury), and experimental autoimmune neuritis, and that pharmacologic inhibition of TNF production reduces pain related behaviors in mice with CCI, and that neutralizing antibodies to TNF-α or other TNF-α inhibitors may have the same effect." *Id.* The Office also argues that Sommer describes "experiments in mice in which ligatures were placed around the sciatic nerve and TAPI was administered by local epineurial injection to the injured nerve." *Id.*

The Office argues that it would have been *prima facie* obvious to the person of ordinary skill in the art at the time the invention was made to use the methods of Amin *et al.* to treat neurological conditions as described in Sommer. The Office further argues that "since Sommer *et al.* teach that inflammatory nerve pain in a disease (i.e. lepromatous leprosy) and in experimental neuropathies results in increased levels of TNF-α, which can be reduced by TNF-α inhibitors, and since many nerve disorders such as spinal cord injury result

in inflammation and increase in TNF-α, the skilled artisan would be motivated to treat any of these nerve disorders/injuries with the method of Amin *et al.*" *Id*; at 7-8. The Office argues that although nucleus pulposus-induced nerve injury may not have been disclosed in the prior art, the method of treatment is inherently the same.

1. Traversal of the Rejection

Applicants respectfully traverse the rejection and assert that a *prima facie* case of obviousness has not been adduced for at least the reasons set forth below. To establish a *prima facie* case of obviousness, the Office must fulfill three requirements. First, the prior art relied upon, coupled with the knowledge generally available in the art at the time of the invention, must contain some suggestion or incentive that would have motivated the skilled artisan to modify a reference or to combine references. *In re Fine*, 837 F.2d 1071, 1074, 5 U.S.P.Q.2d 1596, 1598 (Fed. Cir. 1988). Given the teachings of Amin, there is no motivation to combine these references. Second, the proposed modification of the prior art must have had a reasonable expectation of success, determined from the vantage point of the skilled artisan at the time the invention was made. In other words, a hindsight analysis is not allowed. *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1209, 18 U.S.P.Q.2d 1016, 1023 (Fed. Cir. 1991). Lastly, the prior art reference or combination of references must teach or suggest all the limitations of the claims. *In re Wilson*, 424 F.2d 1382, 1385, 165 U.S.P.Q. 494, 496 (C.C.P.A. 1970). And the teachings or suggestions, as well as the expectation of success, must come from the prior art, and not the applicant's disclosure. *In re Vaeck*, 947 F.2d 488, 493, 20 U.S.P.Q.2d 1348, 1442.

Applicants assert that the artisan of ordinary skill at the time would have had no suggestion or incentive to modify the references to achieved the claimed invention as amended. Accordingly, there could be no expectation of success that this combination would work. The references when viewed alone or in combination do not teach the invention.

Sommer teaches the mechanical deformation by ligation of a nerve until brief twitch in the hind limb of a mouse. The ligated nerve is the sciatic nerve. Sommer at 46. The

sciatic nerve is a peripheral nerve. As discussed in Section IV, the sciatic nerve is not involved in sciatica or nucleus pulposus mediated disorders. These disorders involve nerve roots, which are anatomically quite different than the peripheral nerves. Additionally, sciatica and other nucleus pulposus mediated disorders can occur in the absence of any ligation or mechanical constriction of a nerve. The pathology of sciatica and nucleus pulposus mediated diseases, as discussed in Section IV, is caused by a different mechanism than the experimental model proposed by Sommer or the other diseases listed by Sommer (*e.g.*, constrictive mononeuropathies, nerve crush, chronic constriction nerve injury (CCI), experimental autoimmune neuritis or lepromatous leprosy). As no mechanical deformation of the sciatic nerve is needed for a nucleus pulposus mediated disorder, Sommer does not teach such disorders, let alone provide a method of treating them.

Finally, Sommer only teaches epineurial administration of drugs. *Id.* at 47, col. 2. Epineurial injection is not the same as systemic, oral, intramuscular or intravenous administration. Sommer does not suggest let alone teach other methods of administration. Clearly, there can be no motivation to combine the teachings of Sommer with Amin to administer the drugs in the manners suggested by the Office, as Amin specifically argues that TNF-α inhibitors would not be used to treat neurodegenerative disorders. Although Amin does teach alternative methods of administration, the skilled artisan would not consider that helpful given how Amin teaches away from the claimed invention and Sommer does not teach methods of treating nucleus pulposus mediated disorders.

2. Assertion of Inherent Obviousness

Applicants also assert that an inherency argument tied to an obviousness rejection is improper ("Although nucleus pulposus-induced nerve injury may not have been disclosed in the prior art, the method of treatment is inherently the same."). Office Action, page 8. To establish inherency, extrinsic evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *In re Robertson*, 49 U.S.P.Q.2d 1949, 1951 (Fed Cir. 1999).

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"To serve as an anticipation when the reference is silent about the asserted inherent characteristic, such gap in the reference may be filled with recourse to extrinsic evidence. Such evidence must make clear that the missing descriptive matter is necessarily present in the thing described in the reference, and that it would be so recognized by persons of ordinary skill. *Continental Can Co. USA Inc. v. Monsanto Co.*, 20 U.S.P.Q.2d 1747, 1749 citing to *In re Oelrich*, 666 F.2d 578, 581, 212 U.S.P.Q. 323, 326 (C.C.P.A. 1981). Moreover, "[i]nherency, however may not be established by probabilities or possibilities. The mere fact that a certain thing may result from a given set of circumstances is not sufficient." *Id.* In fact, "the inherency of an advantage and its obviousness are entirely different questions. That which may be inherent is not necessarily known. Obviousness cannot be predicated on what is unknown. *In re Spormann*, 150 U.S.P.Q. 449, 452 (C.C.P.A. 1966). The fact that a certain result or characteristic may occur or be present in the prior art is not sufficient to establish the inherency of that result or characteristic." *In re Rijkaert*, 9 F.3d 1531, 1534, 28 U.S.P.Q.2d 1955, 1957 (Fed. Cir. 1993). That which is inherent in the prior art, if not known at the time of the invention, cannot form a proper basis for rejection the claimed invention as obvious under § 103. *In re Shetty*, 566 F.2d. 81, 86, 195 U.S.P.Q. 753, 756-57 (C.C.P.A. 1977). Stated otherwise, an "expectation of success" (a step required for a reference to render an invention obvious) is a statement of a probability, and a probability cannot be used to establish inherency.

Accordingly, Applicants assert that in view of the teachings of Amin and Sommer both alone and in combination, the extrinsic evidence provided by Sommer does not make clear the missing descriptive matter found in Amin. Additionally, if we reverse the references, the extrinsic evidence provided by Amin would also not make clear the missing descriptive matter found in Sommer. Thus, the combination of the references do not inherently teach the claimed invention. Nor does the combination of references when analyzed under the requirements for 35 U.S.C. § 103 suggestion the claimed invention.

For at least the reasons asserted above and in view of the amendments to the claims, Applicants assert that no *prima facie* case of obviousness has been adduced. Accordingly, the rejection should be withdrawn and the claims allowed.

VII. ADJUSTMENT OF PATENT TERM UNDER 35 U.S.C. § 154

In the event the claims of this application are allowed, Applicants request that the extensions of time requested for responding to the instant Office Action not be deducted from any period of adjustment due to patent office delay calculated under § 154. The extensions taken after the three-month statutory period in which to respond were necessary in view of prosecution in co-pending application U.S.S.N. 09/760,810 (hereinafter the '810 application). The rejections in both cases involved some of the same cited art and were similar, as admitted by the Office. Accordingly, Applicants requested an interview in order to expedite prosecution in both cases and to resolve all outstanding issues in these cases with each of the Examiners, Examiner O'Hara (in the instant application) and Examiner Seharaseyon (in the '810 application). To have responded to the instant application before seeing the rejections issued in the '810 application on March 11, 2003, would have not been in the best interest of forwarding prosecution in either of the applications. Accordingly, the requested extensions of time were necessary for obtaining an interview and forwarding prosecution in both applications. The extension of time allowing Applicants to respond after February 18, 2002 in the instant matter should not be deducted from any adjustment period due to delay on the part of the Office found for the instant application should the application issue.

CONCLUSION

In view of the foregoing, further and favorable action in the form of a Notice of Allowance is believed to be next in order. Such action is earnestly solicited.

In the event that there are any questions relating to this application, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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